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Attitudes towards risk-reducing early salpingectomy with delayed oophorectomy for ovarian cancer prevention: a cohort study

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Objective To determine risk-reducing early salpingectomy and delayed oophorectomy (RRESDO) acceptability and effect of surgical prevention on menopausal sequelae/satisfaction/regret in women at increased ovarian cancer (OC) risk.

Design Multicentre, cohort, questionnaire study (IRSCN:12310993).

Setting United Kingdom (UK).

Population UK women without OC ≥ 18 years, at increased OC risk, with/without previous RRSO, ascertained through specialist familial cancer/genetic clinics and BRCA support groups.

Methods Participants completed a 39-item questionnaire. Baseline characteristics were described using descriptive statistics. Logistic/linear regression models analysed the impact of variables on RRESDO acceptability and health outcomes.

Main outcomes RRESDO acceptability, menopausal sequelae, satisfaction/regret.

Results In all, 346 of 683 participants underwent risk-reducing salpingo-oophorectomy (RRSO). Of premenopausal women who had not undergone RRSO, 69.1% (181/262) found it acceptable to participate in a research study offering RRESDO. Premenopausal women concerned about sexual dysfunction were more likely to find RRESDO acceptable (odds ratio [OR] = 2.9, 95% CI 1.2–7.7,

$P = 0.025$). Women experiencing sexual dysfunction after premenopausal RRSO were more likely to find RRESDO acceptable in retrospect (OR = 5.3, 95% CI 1.2–27.5, $P < 0.031$). In all, 88.8% (143/161) premenopausal and 95.2% (80/84) postmenopausal women who underwent RRSO, respectively, were satisfied with their decision, whereas 9.4% (15/160) premenopausal and 1.2% (1/81) postmenopausal women who underwent RRSO regretted their decision. HRT uptake in premenopausal individuals without breast cancer (BC) was 74.1% (80/108). HRT use did not significantly affect satisfaction/regret levels but did reduce symptoms of vaginal dryness (OR = 0.4, 95% CI 0.2–0.9, $P = 0.025$).

Conclusion Data show high RRESDO acceptability, particularly in women concerned about sexual dysfunction. Although RRSO satisfaction remains high, regret rates are much higher for premenopausal women than for postmenopausal women. HRT use following premenopausal RRSO does not increase satisfaction but does reduce vaginal dryness.

Keywords Acceptability, BRCA, ovarian cancer, risk-reducing early salpingectomy with delayed oophorectomy.

Tweetable abstract RRESDO has high acceptability among premenopausal women at increased ovarian cancer risk, particularly those concerned about sexual dysfunction.

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Introduction

Ovarian cancer (OC) is the leading cause of death from gynaecological malignancies in the UK.¹ An effective OC-screening programme/strategy is not currently clinically available and 10-year survival rates remain poor at ~30%. Familial cancers are responsible for ~10–20% of OC and *BRCA1/BRCA2* mutations account for most of the known hereditary OC risk. *BRCA1/BRCA2* carriers have a 17–44% OC risk and 65–72% breast cancer (BC) risk.^{2–5} *RAD51C/RAD51D/BRIP1* are newer moderate-penetrance OC genes, with lifetime OC risks ~6–13%.^{6–10}

Risk-reducing salpingo-oophorectomy (RRSO) is the most effective method of OC prevention. Traditionally, women at ≥10% lifetime OC risk were deemed high risk and offered risk-management/surgical prevention. Calls for redefining the threshold for surgical prevention have suggested a 4–5% lifetime OC risk,¹¹ as the level demonstrating clinical utility,^{12,13} thus enabling intermediate-risk women to access surgical prevention. This includes those with moderate-penetrance genetic mutations and mutation-negative women with a strong OC family history. In *BRCA*-women, RRSO reduces OC risk by 79–96%.^{14–18} Although initial data suggested that premenopausal RRSO reduced primary BC risk by half,^{16,19,20} recent papers have questioned this.^{21,22} In terms of mortality, RRSO reduces all-cause (HR = 0.40, 95% CI 0.26–0.61), BC-specific (HR = 0.44, 95% CI 0.26–0.76) and OC-specific (HR = 0.25, 95% CI 0.08–0.75) mortality.²⁰ However, RRSO has disadvantages, including major complication rates of 1.5–5%.^{14,23} In premenopausal women, RRSO leads to surgical menopause and infertility. Premature surgical menopause has potential detrimental health sequelae including an increased risk of heart disease, osteoporosis, vasomotor symptoms, neurocognitive decline and sexual dysfunction, especially in women who do not or are unable to use hormone-replacement therapy (HRT).^{24–28} Consequently, some women choose to delay surgery until after menopause, risking a 6- to 16-year mean period of much higher risks of, in particular, high-grade serous OC, especially with *BRCA1*.

With increasing evidence and acceptability of the central role of the fallopian tube in the aetiopathogenesis of epithelial OC, risk-reducing early salpingectomy and delayed oophorectomy (RRESDO) has been proposed as a two-stage surgical alternative to RRSO. RRESDO offers some level of risk reduction to women who decline/wish to delay RRSO while conserving ovarian function and avoiding detrimental consequences of premature menopause.^{29–31} However, prospective outcome data for RRESDO are lacking. The precise level of OC risk reduction and long-term consequences of ovarian function are

unknown. Concerns have been raised regarding the potential attrition from delayed oophorectomy. Therefore, RRESDO is currently recommended in the context of a clinical trial and 80% of UK clinicians support this.³² Trials are currently underway in the UK (PROTECTOR; ISRCTN25173360),³³ the Netherlands (TUBA; NCT02321228)³⁴ and USA (WISP, NCT02760849).³⁵

There is a paucity of international data and a lack of UK data on RRESDO acceptability among high-risk women. A US survey showed that 34.3% (70/204) *BRCA* pathogenic-variant carriers were interested in participating in a study offering RRESDO.³⁶ A Dutch qualitative study investigating barriers and facilitators to RRESDO among *BRCA*-carriers found seriousness of OC, family history (FH), previous BC, uncertainty about the effect of and ease of the decision to undergo RRSO to be barriers.³⁷ The main facilitator was longer maintenance of ovarian function to delay negative effects of premature menopause.³⁷

We present data from a multicentre UK survey in women at increased OC risk, concerning: (1) acceptability of RRESDO, (2) menopausal sequelae following RRSO and (3) satisfaction/regret following RRSO.

Methods

Design

The present study was a multicentre, cohort, questionnaire study (ISRCTN:12310993). Inclusion criteria were: UK women aged ≥18 years, at increased OC risk either due to pathogenic variants in an OC gene (*BRCA1/BRCA2/RAD51C/RAD51D/BRIP1*) or strong FH of OC or BC + OC. A strong FH was defined as ≥2 first-degree relatives with OC in *BRCA1/BRCA2*-negative or untested women. Exclusion criteria were: non-UK residents or women with a personal history of OC. Women with and without previous RRSO were invited.

Participants

Participants were selected via six NHS specialist familial cancer or genetic clinics (Manchester/Cambridge/Barts-London/University-College-London/Guys-London/Dundee) and a patient support group for *BRCA*-carriers (*BRCA-Umbrella*).

Recruitment

All participants provided written consent after review of a detailed participant information-sheet (PIS) along with the option of completing a paper/web-based questionnaire. The PIS (Appendix S1) provided information on current OC-prophylactic surgery available on the NHS (RRSO) and the proposed two-stage surgical alternative (RRESDO), study aims, logistics of participation and contact details of

charities/support groups providing further independent information/support.

The 39-item questionnaire collected socio-demographic, surgical/menstrual/FH and health consequences of premature menopause influencing decisions to undergo/delay/decline premenopausal RRSO (Likert scale) data for all participants. Individuals were instructed to complete different sections of the questionnaire depending on whether they had undergone RRSO. Questionnaire items for women who had not undergone RRSO covered: benefits and limitations of RRESDO impacting acceptability of procedure (Likert scale); putative acceptability of undergoing RRESDO ('yes, no, not sure' options), acceptability of participating in a research study offering RRESDO (Likert scale); anticipated timing of future surgery (Likert scale). Questionnaire items for women who had undergone RRSO covered: retrospective acceptability (Likert scale) of undergoing RRESDO had it been available (item only for women who had undergone premenopausal RRSO); HRT use ('yes/no'); menopause sequelae (Likert scale) following RRSO; satisfaction and regret (Likert scale) following RRSO. Respondents could recheck all answers and an optional free-text box was provided for further comments.

Questionnaire development

The 39-item questionnaire (Appendix S2) was developed in several stages. An initial draft was developed following a literature review. Each question was systematically discussed and debated. These were subsequently reviewed by senior clinicians in the fields of gynaecological precision medicine and cancer prevention, and gynaecological oncology. The clinicians gave each item a relevance score from 1 (least relevant) to 4 (most relevant) based on their knowledge and experience. They were also asked to identify any additional questions which they considered important and might be missing. A second consensus meeting was held to review responses to the initial questionnaire, delete low-relevance items and optimise questionnaire length and facilitate compliance. A second pilot of the survey was carried out for readability, ease-of-use and layout. These processes helped ensure content and face optimisation. The final version was further reviewed/commented on, resulting in further rationalisation to a 39-item questionnaire. For questions pertaining to satisfaction/regret with decision making, the validated five-item decision regret scale^{38,39} was used as well as two additional items developed by the panel of clinical experts exploring the impact of familial wishes on decision making.

Statistical analysis

Descriptive statistics were used for baseline characteristics as well as satisfaction/regret questions. Multiple logistic regression was used to model the effect of variables on the

acceptability of undergoing RRESDO (putative acceptability in premenopausal women who had not undergone OC-prevention surgery; retrospective acceptability of RRESDO in women who had undergone premenopausal RRSO), acceptability of taking part in a research study offering RRESDO (premenopausal women not having undergone OC-prevention surgery) and effect of HRT uptake on menopausal sequelae in women who had undergone premenopausal RRSO. Multiple linear regression was used to model the effect of menopausal sequelae on satisfaction/regret following premenopausal RRSO, and association of HRT use versus non-use was also explored. Multiple analyses were adjusted for marital status, ethnicity, education, income, FH of OC/BC, risk-reducing mastectomy (RRM) and personal history of BC. Wilcoxon's rank-sum test and Fisher's exact test were used to test the hypothesis about differences in means and proportions, respectively. Two-sided *P*-values are reported for all statistical tests. Statistical analysis used R version 3.5.1 (Lucent Technologies, Murray Hill, NJ, USA).

Patient and public involvement (PPI)

The RRESDO study team undertook extensive stakeholder engagement before study commencement. Groups involved included healthcare professionals and *BRCA* support groups. This was essential to ensure stakeholder management, increase engagement and awareness and facilitate development and delivery of study. These groups provided input to the Patient Information Sheet and also served as an independent point of contact for more information on the study. Support groups helped increase study awareness through their websites/newsletters. They will also be involved in dissemination of study findings following publication.

Core outcome sets

There are no core outcome sets for surgical prevention at present.

Results

Between October 2017 and June 2019, 773 individuals completed the paper/online-questionnaire. Of these, 90 were excluded because they did not meet the eligibility criteria. The remaining 683 individuals were included in the analysis. Table 1 summarises baseline cohort characteristics. In all, 337/683 (49.3%) respondents had not undergone RRSO and 346/683 (50.7%) had. Women who had not undergone RRSO were significantly younger than women who had (38.3 versus 51.5 years, $P \leq 0.001$).

Table 2 summarises RRESDO acceptability. Among premenopausal women who had not undergone RRSO, the overall RRESDO acceptability ('yes') was 55.3% (145/262) and the overall unacceptability ('no') was 20.2% (53/262);

Table 1. Baseline characteristics of cohort

	No RRSO <i>n</i> = 337, 49.3%	RRSO <i>n</i> = 346, 50.7%	<i>P</i> -value
Mean age in years (SD, range)	38.25 (10.23, 19–81)	51.53 (9.56, 26–81)	<0.001
Mean parity (SD, range)	1.92 (0.83, 1–6)	2.18 (0.86, 1–7)	<0.001
Nulliparous	217/336, 64.6	286/343, 83.4	<0.001
Premenopausal/premenopausal at time of RRSO	262/335, 78.2	164/248, 66.1	0.001
Postmenopausal/postmenopausal at time of RRSO	73/335, 21.8	84/248, 33.9	0.001
Family complete	194/331, 58.6	318/334, 95.2	<0.001
High risk of OC			
<i>BRCA1</i> carrier	157/337, 46.6	162/346, 46.8	1
<i>BRCA2</i> -carrier	171/337, 50.7	161/346, 46.5	0.284
<i>BRCA1</i> - and <i>BRCA2</i> -carrier	5/337, 1.5	7/346, 2.0	0.773
Intermediate risk of OC			
<i>RAD51C</i> -carrier	0/337, 0.0	1/346, 0.3	
<i>BRIP1</i> -carrier	3/337, 0.9	1/346, 0.3	0.367
<i>BRCA1/BRCA2</i> -negative but strong FH of OC	1/337, 0.3	2/346, 0.6	1
<i>BRCA1/BRCA2</i> untested but strong FH of OC	1/337, 0.3	3/346, 0.9	0.624
Unsure of genetic test result	4/337, 1.2	6/346, 1.7	0.752
Personal history of BC	77/337, 22.8	160/346, 46.2	<0.001
Personal history of other cancers	6/337, 1.8	9/346, 2.6	0.604
Therapeutic mastectomy	20/337, 5.9	47/346, 13.6	0.001
Risk-reducing mastectomy	70/337, 20.8	143/346, 41.3	<0.001
Breast surgery for benign breast pathology	0/337, 0.0	4/346, 1.2	
Cosmetic breast surgery	2/337, 0.6	1/346, 0.3	0.620
Marital status			
Single, divorced, separated, widowed	72/332, 21.7	36/341, 10.6	<0.001
Married, cohabiting/living with partner	260/332, 78.3	305/341, 89.4	<0.001
Ethnicity			
Caucasian	301/334, 90.1	300/341, 88.0	0.391
Non-caucasian	33/334, 9.9	41/341, 12.0	0.391
Education			
PhD, Masters, Bachelor's degree	199/329, 60.5	141/336, 42.0	<0.001
NVQ4, A-level/NVQ3, NVQ1/NVQ2, GCSE/O-level/CSE, no formal qualification	130/329, 39.5	195/336, 58.0	<0.001
Total household income			
≥£30 000	236/325, 72.6	208/312, 66.7	0.121
<£30 000	89/325, 27.4	104/312, 33.3	0.121

BC, breast cancer; FH, family history; OC, ovarian cancer; RRSO, risk-reducing salpingo-oophorectomy.

90/773 participants were excluded because they were at population-level risk of ovarian cancer. 683 participants eligible for analysis.

24.4% (64/262) were 'not sure'. When premenopausal women who had not undergone RRSO were asked whether they would consider taking part in a research study offering RRESDO, overall acceptability (those who responded 'probably, maybe') was 69.1% (181/262) and 30.9% (81/262) found it unacceptable ('probably not, definitely not'). Table 2 provides further details. Multiple logistic-regression model outputs showing the association of covariates with acceptability of undergoing RRESDO ('yes' versus 'no') among premenopausal women who have not undergone RRSO are given in Table 3. Genetic-mutation type or carrier-status/FH/knowledge of tubal origin/future OC-prevention surgery plans/childbearing/ethnicity/education/income did not statistically significantly affect RRESDO acceptability. However,

premenopausal women who were more concerned about sexual dysfunction were three times more likely to find undergoing RRESDO acceptable than were those less concerned about sexual dysfunction (OR = 2.9, 95% CI 1.2–7.6, $P = 0.025$). When considering potential benefits, individuals wanting to delay hot flushes (OR = 5.0, 95% CI 1.2–21.2, $P = 0.025$) were five times more likely to find RRESDO acceptable. When considering acceptability ('yes' versus 'no') of potential limitations of RRESDO, women who found the risks of undergoing two surgeries (OR = 444.1, 95% CI 28–22815, $P \leq 0.001$), interval-monitoring (CA125/USS) between surgeries (OR = 59.0, 95% CI 4.2–1548.7, $P = 0.006$), uncertainty around level of OC risk reduction with RRES (OR = 14.6, 95% CI 1.9–160.6, $P = 0.015$), and

developing an interval OC between the two surgeries (OR = 9.6, 95% CI 1.4–93.7, $P = 0.032$) as acceptable, were more likely to find undergoing RRESDO acceptable. The wide confidence intervals reflect having too few responses from premenopausal women who have not undergone RRSO for certain questionnaire items (acceptability of undergoing two surgeries/interval monitoring/uncertain OC risk reduction/developing interval OC). Multiple logistic-regression model outputs showing association of covariates with acceptability of undergoing RRESDO ('not sure' versus 'no') are given in Table S1. Premenopausal women who had not undergone RRSO and who responded 'not sure' were more likely than women who responded 'no' to find the two-stage aspect of RRESDO acceptable (OR = 6.7, 95% CI 1.6–34.0, $P = 0.013$) and to find interval monitoring (CA125/USS) between the two surgeries acceptable (OR = 8.9, 95% CI 1.5–71.8, $P = 0.025$). Lower acceptability of precision of OC risk reduction following RRES (OR = 0.2, 95% CI 0.1–0.4, $P < 0.0005$) was the predominant factor affecting premenopausal women who were 'not sure' about undergoing RRESDO compared with those responding 'yes'. When asked about the acceptability of complication rates, 157 (80.1%) premenopausal women found the complication rate with two procedures acceptable; 125 (87.4%) women who would undergo RRESDO found this acceptable versus 32 (60.4%) women who would not undergo RRESDO.

When women who had undergone premenopausal RRSO were asked whether they would have considered undergoing RRESDO instead of RRSO had it been offered (retrospective acceptability), 38.4% (61/159) and 61.6% (98/159) responded 'probably/maybe' and 'probably not/definitely not', respectively (Table 2). Multiple logistic-regression model outputs showing association of covariates with retrospective RRESDO acceptability following premenopausal RRSO are given in Table 4. Genetic-mutation type or carrier-status/FH/prior knowledge of tubal origin of OC/ethnicity/education/income did not statistically significantly affect retrospective acceptability of undergoing RRESDO. Following premenopausal RRSO, women who experienced night sweats (OR = 13.8, 95% CI 1.7–140.2, $P = 0.018$), sleep disturbance (OR = 18.8, 95% CI 3.2–160.1, $P = 0.003$), sexual dysfunction (OR = 5.3, 95% CI 1.2–27.5, $P = 0.031$) or urinary incontinence (OR = 17.2, 95% CI 4–98.6, $P < 0.001$) regretted their decision to undergo RRSO (OR = 6.4, 95% CI 1.3–40.7, $P = 0.032$); they also felt the decision to undergo RRSO did them a lot of harm (OR = 3.9, 95% CI 1.2–12.8, $P = 0.022$) and were statistically significantly more likely to have chosen retrospectively to undergo RRESDO instead of RRSO had it been available. However, women who experienced hot flushes (OR = 0.1, 95% CI 0–0.6, $P = 0.013$), osteoporosis (OR = 0.3, 95% CI 0.1–0.9, $P = 0.045$) or fatigue (OR = 0.01, 95% CI 0–0.1, $P < 0.001$) following premenopausal RRSO were

Table 2. RRESDO acceptability

Acceptability	n (%)
Acceptability of undergoing RRESDO among premenopausal women who have not undergone RRSO	
Yes	145/262 (55.34)
No	53/262 (20.23)
Not sure	64/262 (24.43)
Acceptability of participating in a research study offering RRESDO among premenopausal women who have not undergone RRSO	
Probably	95/262 (36.26)
Maybe	86/262 (32.82)
Probably not	48/262 (18.32)
Definitely not	33/262 (12.60)
Retrospective acceptability of RRESDO among women who have undergone premenopausal RRSO	
Probably	28/159 (17.61)
Maybe	33/159 (20.75)
Probably not	46/159 (28.93)
Definitely not	52/159 (32.70)

RRESDO, risk-reducing early salpingectomy with delayed oophorectomy; RRSO, risk-reducing salpingo-oophorectomy.

statistically significantly less likely to have chosen to have undergone RRESDO instead of RRSO retrospectively.

Overall, HRT use among premenopausal women post-RRSO was 53.7% (88/164). However, when stratified by BC status at the time of premenopausal RRSO, the HRT uptake was 74.1% (80/108) among BC-unaffected and 14.3% (8/56) among BC-affected individuals. The mean age at premenopausal RRSO was 47.2 (SD = 6.7) years and the mean duration of HRT use was 4.2 (SD = 3) years. No woman who had undergone postmenopausal RRSO used HRT. The multiple logistic-regression model explored the association of covariates with HRT use versus non-use following premenopausal RRSO. Women with a university level (versus below university) education (OR = 3.1, 95% CI 1.2–8.5, $P = 0.021$) and women who were aware/concerned about neurocognitive decline (OR = 11.2, 95% CI 1.2–136.8, $P = 0.045$) were significantly more likely to use HRT. There was no difference in HRT use versus non-use in women who had undergone premenopausal RRSO who were experiencing sexual dysfunction.

Table S2 reports satisfaction/regret with the RRSO decision making by menopausal status at the time of surgery. There was high satisfaction ('agree/strongly agree' responses) among women who had undergone premenopausal and postmenopausal RRSO (88.82% [143/161] and 95.24% [80/84], respectively, $P = 0.635$) and a similarly high proportion would make the same decision again (87.6% [141/161] versus 94% [79/84], $P = 0.186$). When compared with women undergoing postmenopausal RRSO, those undergoing

premenopausal RRSO had a statistically significantly higher regret rate (respectively 9.4% [15/160] versus 1.2% [1/81], $P = 0.008$) and were more likely to feel that RRSO did them a lot of harm (11.25% [18/160] versus 5% [4/80], $P = 0.006$). Multiple linear-regression modelling showed that HRT use did not statistically significantly affect satisfaction/regret levels in premenopausal women. Correlation analysis did not find a statistically significant association between satisfaction/regret and age of premenopausal RRSO ($r = -0.085$, $P = 0.292$). Multiple linear-regression model outputs showing an association of menopausal sequelae with satisfaction/regret following premenopausal RRSO are given

in Table S3. Women experiencing menopausal sequelae (sexual dysfunction, night sweats, sleep disturbance, vaginal dryness, urinary incontinence, fatigue, memory loss, mood alterations, negative impact on relationship with partner) were significantly more likely to regret undergoing premenopausal RRSO. The multiple logistic-regression model explored the association of HRT use with non-use on menopausal sequelae after premenopausal RRSO (Table S4). HRT users (compared with non-users) were significantly less likely to experience vaginal dryness (OR = 0.4, 95% CI 0.2–0.9, $P = 0.025$) but the prevalence of other symptoms was not reduced.

Table 3. Factors affecting acceptability of undergoing RRESDO among premenopausal women who have not undergone RRSO

	OR	SE	$P > z $	95% CI
Prior knowledge of tubal origin of OC	1.725	0.376	0.147	0.833–3.655
Personal history of BC	1.184	0.558	0.761	0.404–3.672
Previous RRM	0.647	0.407	0.285	0.286–1.421
Family complete	1.146	0.516	0.792	0.417–3.214
Carrier status	1.788	0.911	0.523	0.273–10.928
Marital status	0.679	0.425	0.362	0.289–1.545
Ethnicity	0.492	0.599	0.237	0.153–1.66
Education	0.876	0.408	0.747	0.388–1.94
Income	1.053	0.177	0.77	0.742–1.492
Timing of future OC prevention surgery	0.286	1.171	0.286	0.014–2.095
Family history				
BC	2.889	0.63	0.093	0.813–9.999
OC	1.019	0.785	0.98	0.214–4.799
BC and OC	0.869	0.867	0.871	0.158–4.835
Concerns over premature menopause sequelae influencing decision to undergo RRESDO				
Hot flushes/night sweats	1.27	0.502	0.634	0.475–3.451
Looking older	0.804	0.5	0.663	0.295–2.131
Decreased libido/other sexual side effects	2.918	0.477	0.025	1.163–7.648
Loss of fertility	1.568	0.608	0.459	0.468–5.208
Osteoporosis	1.931	0.567	0.246	0.628–5.895
Heart disease	0.845	0.625	0.787	0.239–2.832
Dementia/memory dysfunction	2.435	0.67	0.184	0.67–9.495
Impact on survival	0.488	0.511	0.16	0.17–1.281
Acceptability of having to take HRT until 51 years	1.501	0.437	0.353	0.64–3.586
Potential benefits of RRESDO influencing decision to undergo RRESDO				
Reduces risk of OC without premature menopause	9.007	1.195	0.066	1.149–192.856
Inspection of tubes/ovaries by doctor	2.323	0.798	0.291	0.474–11.476
delays hot flushes, night sweats	5.028	0.719	0.025	1.218–21.172
delays osteoporosis	1.08	1.332	0.954	0.083–17.385
delays potential change to sexual function	2.945	0.735	0.142	0.682–12.753
Not associated with increased risk of heart disease	1.279	1.127	0.827	0.114–11.238
Potential limitations of RRESDO influencing decision to undergo RRESDO				
Two staged surgery	444.078	1.672	<0.001	*28.04–22814.9
Potential premature menopause	1.939	0.888	0.456	0.348–12.145
Increased complication rate	0.78	1.014	0.807	0.091–5.333
Interval monitoring between surgeries	59.027	1.471	0.006	4.221–1548.671*
Additional time in hospital	0.028	1.94	0.065	0–1.081
Additional time off work for surgery/post-operative recovery	6.166	1.453	0.21	0.406–139.284

Table 3. (Continued)

	OR	SE	P > z	95% CI
Precise level of OC risk reduction with ES unknown	14.556	1.095	0.015	1.961–160.637
Developing an interval OC between the two surgeries	9.554	1.05	0.032	1.405–93.72

BC, breast cancer; FH, family history; HRT, hormone replacement therapy; OC, ovarian cancer; RRESDO, risk-reducing early salpingectomy with delayed oophorectomy; RRM, risk-reducing mastectomy.

Multiple logistic regression analysis on factors affecting acceptability of undergoing RRESDO ('yes' versus 'no' responses) in 198 premenopausal women who have not undergone RRSO. Model adjusted for marital status, ethnicity, education, income, family history of ovarian cancer/breast cancer, risk-reducing mastectomy and personal history of breast cancer.

Prior knowledge of tubal origin of OC: 'yes' versus 'no'; personal history of BC: 'yes' versus 'no'; previous RRM: 'yes' versus 'no'; family complete: 'no' versus 'yes'; carrier status: BRCA1/BRCA2 versus intermediate risk (RAD51C carrier/RAD51D carrier/BRIP1 carrier/BRCA negative but strong FH of OC/BRCA untested but strong FH of OC); marital status: in a relationship (married, cohabiting/living with partner) versus not in a relationship (single, divorced, separated, widowed); ethnicity: non-caucasian versus caucasian; education: university level education (PhD, Masters, Bachelor's degree) versus below university level education (NVQ4, A-level/NVQ3, NVQ1/NVQ2, GCSE/O-level/CSE, no formal qualification); timing of future OC prevention surgery: planning surgery now/within 5 years versus not planning surgery; FH BC (FH of BC alone plus FH of BC and OC): 'yes' versus 'no'; FH OC (FH of OC alone plus FH of OC and BC): 'yes' versus 'no'; FH BC and OC: 'yes' versus 'no'; hot flushes/night sweats: 'yes' versus 'no'; looking older: 'yes' versus 'no'; decreased libido/other sexual side effects: 'yes' versus 'no'; loss of fertility: 'yes' versus 'no'; osteoporosis (self-reported): 'yes' versus 'no'; heart disease: 'yes' versus 'no'; dementia/memory dysfunction: 'yes' versus 'no'; impact on survival: 'yes' versus 'no'; acceptability of having to take HRT until 51 years: 'yes' versus 'no'; reduces risk of OC without premature menopause: 'yes' versus 'no'; inspection of tubes/ovaries by doctor: 'yes' versus 'no'; delays hot flushes/night sweats: 'yes' versus 'no'; delays osteoporosis: 'yes' versus 'no'; delays potential change to sexual function: 'yes' versus 'no'; not associated with increased risk of heart disease: 'yes' versus 'no'; two-stage surgery: 'yes' versus 'no'; potential premature menopause: 'yes' versus 'no'; increased complication rate: 'yes' versus 'no'; interval monitoring between surgeries: 'yes' versus 'no'; additional time in hospital: 'yes' versus 'no'; additional time off work for surgery/postoperative recovery: 'yes' versus 'no'; precise level of OC risk reduction with ES unknown: 'yes' versus 'no'; developing an interval OC between the two surgeries: 'yes' versus 'no'.

*Extreme value of some upper limits of confidence intervals indicate that there were too few responses in some categories of responses.

Table S5 reports the prevalence of menopausal sequelae following pre- and postmenopausal RRSO. The prevalence of sequelae in premenopausal women ranged from 50 to 74.1%, with 66.3% of women experiencing sexual dysfunction and 66.9–74.1% experiencing hot flushes/night sweats/sleep disturbance. Symptoms were significantly more frequent following premenopausal than following menopausal RRSO (Table S5).

Discussion

Main findings

Putative acceptability of undergoing RRESDO among premenopausal women who have not undergone OC prevention surgery is 55.3%, and 69.1% would find participating in a research study offering RRESDO acceptable. Premenopausal women who have not undergone OC-prevention surgery and were concerned about/wanted to delay sexual dysfunction were statistically significantly more likely to find undergoing RRESDO acceptable and participate in a research study offering RRESDO. Similarly, women who had undergone premenopausal RRSO and experienced sexual dysfunction/vasomotor symptoms/urinary incontinence were significantly more likely to regret their decision and find RRESDO acceptable retrospectively. In all, 38.4% of women who

underwent premenopausal RRSO would retrospectively have found RRESDO acceptable were it an option. Although satisfaction with undergoing RRSO was high (premenopausal RRSO = 88.82%, postmenopausal RRSO = 95.24%) for women undergoing premenopausal RRSO, 9.38% regretted their decision and 11.25% felt it did them a lot of harm. Our data suggest good HRT compliance, with 74% of BC-unaffected women using HRT until the recommended age of 51. HRT use did not statistically significantly affect satisfaction/regret levels or alleviate menopausal symptoms except vaginal dryness among women undergoing premenopausal RRSO. There was a higher prevalence of menopausal sequelae following premenopausal RRSO. Women who experienced menopausal sequelae following premenopausal RRSO had higher regret levels.

Strengths and weaknesses

Strengths include that participants were informed in detail about OC-prevention surgery with a detailed participant information-sheet prior to completing our questionnaire; ours is the only study to have generated UK data on RRESDO acceptability and menopausal sequelae/satisfaction/regret following RRSO and it is the largest study internationally reporting RRESDO acceptability. Limitations include that the proportions of individuals with a

Table 4. Factors associated with retrospective acceptability of RRESDO among women who have undergone premenopausal RRSO

	OR	SE	<i>P</i> > z	95% CI
Prior knowledge of tubal origin of ovarian cancer	1.514	0.444	0.35	0.63–3.625
Personal history of breast cancer	0.731	0.468	0.504	0.289–1.824
Previous risk reducing mastectomy	0.618	0.456	0.291	0.249–1.5
Carrier status	1.626	0.898	0.589	0.31–12.385
Marital status	0.716	0.458	0.466	0.291–1.768
Ethnicity	1.184	0.635	0.791	0.321–4.058
Education	1.11	0.398	0.793	0.507–2.433
Income	1.079	0.194	0.695	0.739–1.589
FH				
BC	1.445	0.896	0.682	0.281–11.041
OC	1.754	1.120	0.616	0.198–18.561
BC and OC	0.944	1.166	0.961	0.083–9.194
Experienced menopausal sequelae following RRSO				
Hot flushes	0.09	0.955	0.013	0.013–0.566
Night sweats	13.76	1.108	0.018	1.729–140.177
Sleep disturbance	18.78	0.988	0.003	3.186–160.144
Vaginal dryness	0.76	0.658	0.671	0.204–2.774
Sexual dysfunction	5.34	0.779	0.031	1.244–27.467
Loss of fertility	0.70	0.669	0.587	0.174–2.501
Osteoporosis	0.25	0.700	0.045	0.057–0.919
Urinary incontinence	17.20	0.807	<0.001	3.985–98.597
Fatigue	0.01	1.150	<0.001	0.001–0.096
Memory loss	0.67	0.662	0.541	0.177–2.45
Mood alterations	3.06	0.684	0.102	0.834–12.654
Impact on relationship with partner	1.81	0.676	0.379	0.49–7.158
Satisfaction/regret following RRSO				
I regret the choice that was made	6.385	0.866	0.032	1.251–40.746
I would make the same decision if I had to do it over again	0.471	4.597	0.87	0.001–205.952
The decision did me a lot of harm	3.877	0.590	0.022	1.226–12.795
I was directly influenced by the direct wishes of my family	3.762	0.700	0.058	0.974–15.615
I was influenced by the unexpressed wishes of my family	0.401	0.734	0.212	0.089–1.631

BC, breast cancer; FH, family history; HRT, hormone replacement therapy; OC, ovarian cancer; RRESDO, risk-reducing early salpingectomy with delayed oophorectomy; RRM, risk-reducing mastectomy.

Multiple logistic regression analysis on factors affecting retrospective acceptability ('probably, maybe' versus 'probably not, definitely not' responses) of undergoing RRESDO had it been an option in 159 women who have undergone premenopausal RRSO. Model adjusted for marital status, ethnicity, education, income, family history of ovarian cancer/breast cancer, risk-reducing mastectomy and personal history of breast cancer. Prior knowledge of tubal origin of OC: 'yes' versus 'no'; personal history of BC: 'yes' versus 'no'; previous RRM: 'yes' versus 'no'; family complete: no versus yes; carrier status: BRCA1/BRCA2 versus intermediate risk (RAD51C carrier/RAD51D carrier/BRIP1 carrier/BRCA-negative but strong FH of OC/BRCA untested but strong FH of OC); marital status: in a relationship (married, cohabiting/living with partner) versus not in a relationship (single, divorced, separated, widowed); ethnicity: non-caucasian versus caucasian; education: university level education (PhD, Masters, Bachelor's degree) versus below university level education (NVQ4, A-level/NVQ3, NVQ1/NVQ2, GCSE/O-level/CSE, no formal qualification); timing of future OC prevention surgery: planning surgery now/within 5 years versus not planning surgery; FH BC (FH of BC alone plus FH of BC and OC): 'yes' versus 'no'; FH OC (FH of OC alone plus FH of OC and BC): 'yes' versus 'no'; FH BC and OC: 'yes' versus 'no'; hot flushes: 'yes' versus 'no'; night sweats: 'yes' versus 'no'; sleep disturbance: 'yes' versus 'no'; vaginal dryness: 'yes' versus 'no'; sexual dysfunction: 'yes' versus 'no'; loss of fertility: 'yes' versus 'no'; osteoporosis (self-reported): 'yes' versus 'no'; urinary incontinence: 'yes' versus 'no'; fatigue: 'yes' versus 'no'; memory loss: 'yes' versus 'no'; mood alterations: 'yes' versus 'no'; impact of relationship with partner: 'yes' versus 'no'; it was the right decision: 'yes' versus 'no'; I regret the choice that was made: 'yes' versus 'no'; I would make the same decision if I had to do it over again: 'yes' versus 'no'; the decision did me a lot of harm: 'yes' versus 'no'; the decision was a wise one: 'yes' versus 'no'; I was directly influenced by the direct wishes of my family: 'yes' versus 'no'; I was influenced by the unexpressed wishes of my family: 'yes' versus 'no'.

university degree/household income of \geq UK£ 30,000 were higher than the UK national average and 88% of our cohort were caucasian. Consequently, these results may not be generalisable to a minority, lesser educated/affluent

population of *BRCA*-carriers. Also, because only 1.77% (12/683) of our cohort were at intermediate OC risk, no inferences can be drawn for this subgroup. In addition, questionnaire responses may have been affected by recall

bias. We excluded women with a previous history of OC so as not to bias results, as they do not reflect unaffected women considering prophylactic OC-surgery.

Interpretation

A US survey-study reported 34.3% (70/204) acceptability in taking part in a research study offering RRESDO among premenopausal women who had not undergone RRSO.³⁶ This is lower than the 69.1% (181/262) we found, despite both cohorts being similar in terms of baseline demographics (mean age 38.25 versus 35.4 years; 88 versus 90.7% caucasian, personal history of BC 22.8 versus 16.7%) and our cohort having more nulliparous women (64.6 versus 41.2%). Differences in healthcare systems (UK state-funded versus US-privatised/insurance-based) and increasing awareness may have contributed to the dissimilar findings. In the USA, 32.8% (20/61) of women not interested in participating in a research study offering RRESDO, cited concerns related to additional healthcare costs as their reason to decline participation.³⁶

The lack of a precise level of OC risk-reduction data with ES was an important limitation for premenopausal women who had not undergone OC-prophylactic surgery and who did not find RRESDO acceptable. Additionally, impaired sexual function, as a direct consequence of premenopausal-oophorectomy, is an extremely important consideration for women who have not undergone surgical prevention. There are currently three trials open to recruitment, investigating aspects of RRESDO.⁴⁰ The UK trial PROTECTOR³³ and US trial WISP³⁵ are both powered on sexual function and will provide valuable information on the impact of RRESDO on sexual function. That women experiencing night sweats/urinary incontinence/sexual dysfunction were significantly more likely to find RRESDO acceptable but those experiencing other symptoms might not, suggests there is a range of tolerability and acceptability of various symptoms among women which affects surgical decision making.

Our data show 50.7% (346/683) RRSO uptake, which is consistent with literature reports of 12–78%.^{14,24,27,36,41–68} Uptake was higher among older women, women who completed childbearing, those who had BC themselves, and those having undergone RRM. This is in keeping with published data.^{41,44,47,50,57,62,69,70}

Offering RRESDO to premenopausal women who have completed childbearing may reduce uptake of premenopausal RRSO. This is supported by our data, which show that 38.4% of women who had undergone premenopausal RRSO would have in retrospect found RRESDO acceptable had it been an option. However, RRESDO may increase the overall number of women undergoing premenopausal OC surgical prevention, as it offers an alternative option to individuals otherwise

declining premenopausal oophorectomy due to the negative consequences of premature menopause.

Satisfaction following RRSO in *BRCA*-carriers is reported to be high at 86–97% at 1–3 years post-surgery,^{27,46,66,71,72} which is in keeping with our results. However, 9.4% (15/150) women in our cohort who underwent premenopausal RRSO regretted their decision, which is higher than the 5–7% reported 2–3 years post-RRSO in the literature.^{27,71} Our data show a positive correlation between regret and menopausal sequelae following surgery. However, these results must be interpreted with caution in light of the small number of women ($n = 15$) who reported regret. There are no published data on the effect of HRT on satisfaction/regret following RRSO. Our results show that HRT use did not statistically significantly affect satisfaction/regret levels in women who had undergone premenopausal RRSO despite a high HRT uptake of 74.1% in BC-unaffected women who have undergone premenopausal RRSO. HRT uptake in women undergoing premenopausal RRSO is reported to be 8–75% in the literature.^{28,72–75} Although our reported uptake is at the upper end of this range, it may not be a true reflection of practice in the UK. We acquired our data through specialist familial cancer clinics which manage women in a multidisciplinary setting that includes routine counselling on the detrimental health sequelae of premature menopause along with the importance of HRT in mitigating these risks and input/access to menopause specialists for symptom and sequelae management. A large proportion of UK women at increased OC risk are managed in non-specialist settings and may receive inconsistent menopause management advice.⁷⁶ Short-term HRT use following premenopausal RRSO in unaffected *BRCA1/BRCA2*-carriers is beneficial.^{77–80} Premenopausal women should be involved in formulating an individualised pre-surgical menopause symptom management and HRT-plan and fully counselled regarding the consequences of iatrogenic menopause, treatment benefits and its efficacy in alleviating vasomotor symptoms and sexual dysfunction. This needs to be discussed as part of informed consent and incorporated into the RRSO decision-making process.

Contrary to our data, the literature shows that HRT use following premenopausal RRSO reduces the prevalence and severity of hot flushes.^{28,75,81,82} However, consistent with our data, according to the literature, HRT use following premenopausal RRSO reduces vaginal dryness but does not alleviate sexual dysfunction (sexual pleasure/habit/satisfaction/libido).^{28,72,75,81}

The literature reports that women undergoing premenopausal RRSO experience a significant worsening of endocrine symptoms (hot flushes/night sweats/sweating).⁷² However, the literature on endocrine symptoms following postmenopausal RRSO is conflicting with different studies reporting either no increase⁷² or increase in the prevalence

of endocrine symptoms.²⁷ In our study, baseline levels of menopausal sequelae symptoms prior to premenopausal and postmenopausal RRSO were not recorded, and although our data show a prevalence of 66.9–74.1% and 25.4–40.7% of endocrine symptoms following pre- and postmenopausal RRSO, respectively, we cannot be certain some symptoms were not already present prior to RRSO or whether they worsened following surgery, particularly in postmenopausal women.

Conclusion

Acceptance of the central role of the fallopian tube in aetiopathogenesis of OC and health consequences of premature menopause from oophorectomy has led to RRESDO being proposed as a surgical alternative for premenopausal women whose family is complete but who decline/delay oophorectomy. Given lack of data on long-term health, the extent of OC risk reduction and concerns over attrition, RRESDO is currently recommended only within the context of a research trial. A total of 69.1% of UK women who have not undergone premenopausal oophorectomy and particularly women concerned about sexual dysfunction would find it acceptable to participate in a research study offering RRESDO. Although RRSO remains the gold standard for OC prevention, ~10% who undergo premenopausal RRSO regret their decision, particularly due to menopausal sequelae. HRT uptake is good in women managed in specialist centres. Although HRT use has been shown to mitigate some endocrine symptoms, it does not appear to alleviate sexual dysfunction or increase satisfaction levels following RRSO. Women at increased OC risk contemplating OC-prevention surgery may be better managed in a multidisciplinary setting of specialist familial cancer clinics with input from gynaecologists/psychologists/menopause/fertility specialists with links to genetics teams.

Disclosure of interests

RM declares research funding from Barts & the London Charity and Eve Appeal outside this work, an honorarium for grant review from Israel National Institute for Health Policy Research and honorarium for advisory board membership from AstraZeneca/MSD. RM is supported by an NHS Innovation Accelerator (NIA) Fellowship for population testing. UM has a financial interest in Abcodia, Ltd., a company formed to develop academic and commercial development of biomarkers for screening and risk prediction. DGE declares honoraria for advisory board membership from AstraZeneca. The other authors declare no conflict of interest. Completed disclosure of interest forms are available to view online as supporting information.

Contribution to authorship

Conception: RM. Design & development: FG, RM. Questionnaire development: FG, DC, CG, UM, RL, RM. Data collection: FG, DC, MO, SG, RM, LI, VT, IE, LM, KR, RC, GE. Data analysis: FG, OB, RM. Preparation of tables: FG, OB. Initial draft of manuscript: FG, RM. Manuscript writing, review and approval: All authors.

Details of ethics approval

The RRESDO Survey study received full ethics approval from West Midlands – Edgbaston Research Ethics Committee on 21 August 2017 (REC Reference number 17/WM/0324). The study was registered with the International Standard Randomized Controlled Trial Number Register – ISRCTN 12310993 (<https://doi.org/10.1186/ISRCTN12310993>). All study volunteers provided written informed consent to participate in the study.

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Data sharing

Relevant anonymised data can be obtained on reasonable request from the corresponding author.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Factors affecting 'not sure' versus 'no' questionnaire responses on acceptability of undergoing RRESDO among premenopausal women who have not undergone RRSO.

Table S2. Satisfaction and regret according to menopausal status at the time of RRSO.

Table S3. Effect of menopausal sequelae on satisfaction and regret among women who have undergone premenopausal RRSO.

Table S4. Effect of HRT use versus non-use on menopausal sequelae in women who have undergone premenopausal RRSO.

Table S5. Prevalence of menopausal sequelae by menopausal status at the time of RRSO.

Appendix S1. Participant information sheet: Views of women at high risk of ovarian cancer towards removal of fallopian tubes for ovarian cancer prevention.

Appendix S2. Survey to determine attitudes of women at increased risk of ovarian cancer towards risk-reducing early salpingectomy with delayed oophorectomy for ovarian cancer prevention. ■

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